Review of the Draft Public Health Goal for 1,2,3-Trichloropropane in Drinking Water

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Issue #1 – Accuracy of the Information Presented: The information presented on toxicity, metabolism, modes of action, and the potential for carcinogenicity and reproductive toxicity was accurate. With regard to exposure, the Public Health Goal (PHG) document failed to discuss the published data on TCP emission from shower water which indicates much lower TCP inhalation exposure during showering than assumed in the PHG document. This issue is discussed under Issue #5.

Issue #2 – Appropriateness of the Approach: Overall, the approach used in developing the PHG document with regard to toxicology data was appropriate. However, the approach used to estimate non-drinking water exposure was entirely opaque. On page 6, the document states that the CALTOX multimedia exposure model "to determine if inhalation and dermal exposure to 1,2,3-trichloropropane, mainly during showering, would be expected to substantially add to the daily exposure …". Given that the general structure of the model as applied to residential TCP exposure was not described, and that all model inputs were not identified, one cannot judge the reliability of the conclusion drawn from the model output, namely, that inhalation exposure is essentially equivalent to ingesting another 2 L/day of water containing TCP. The document's emphasis was clearly the derivation of carcinogenic potency and the acceptable daily dose for non-cancer health outcomes. Because human health risk depends on dose, a more transparent estimation of exposure (and dose) is required.

Issue #3 – Data Evaluation and Interpretation: The PHG document identified the key studies concerning TCP, and appropriately used the animal data in a dose-response assessment. I note that using a "middle position" of treating the carcinomas as fatal and the papillomas and adenomas as incidental to the cause of animal death was reasonable.

Issue #4 – Appropriateness of the Risk Assessment Methodology Used: I offer comments related to estimating carcinogenic potency and non-drinking water exposure.

Comment 2 Estimating TCP Carcinogenic Potency: The document needs to better justify the reliance on the forestomach carcinoma data because: (1) humans do not have a forestomach, and (2) in Table 6 which reports the time-to-tumor modeling results, the q_1^* estimates based on other tissue sites (liver, mammary gland, oral cavity, pancreas, uterus) are 14- to 125-fold lower than the estimate $q_1^* = 25\ (\text{mg/kg-day})^{-1}$ based on the female mouse fore-stomach. It is certainly more health conservative to base the analysis on "the most sensitive cancer endpoint" (forestomach carcinoma induction), but at face value it does not seem biologically appropriate.

Related to the appropriate tissue site is the 1996 La, et al., study finding (Toxicology and Applied Pharmacology, Vol. 140, pp 108-114) that the gavage bolus dose method (used in the NTP study) versus the drinking water dose method in mice produced higher concentrations of DNA adducts, and also caused increased cell proliferation not observed with the drinking water dosing route. The PHG document described the La, et al., study on pages 12 and 13. As stated in the 2006 CICAD 56 for TCP: "It appears that the high local concentrations to be expected from the gavage bolus dose led to significant adduct formation and cell proliferation in contrast to the continuous but lower local concentrations resulting from drinking-water exposure. Consequently, it has to be expected that gavage exposure will overestimate the carcinogenic potency of 1,2,3-trichloropropane. A number of chemicals, including the structurally related 1,2-dibromo-3-chloropropane, are also known to induce high incidences of forestomach tumors, but only when administered via gavage." These statements reflect the ideas put forward in the 1996 La, et al., article.

One would expect that the high local concentration effect due to gavage dosing would be much diluted in other tissues (liver, mammary gland, pancreas, uterus) compared to the forestomach; in turn, neoplasms at these other tissue sites may be better cancer endpoints. Curiously, the La, et al., study found that gavage dosing caused more DNA adduct formation and cell proliferation in the mouse liver and kidney than in the forestomach. In addition, incidence of carcinomas in the NTP study was highest in the mouse forestomach, not significantly increased in the mouse liver, and not observed in the mouse kidney. This circumstance likely led the authors of the PHG document to dismiss the La, et al., findings. On page 13, the document stated: "In ... [the La, et al.] study, neither adduct formation nor cell proliferation appeared to be predictive of the tumorigenic response observed in the NTP bioassay." On the other hand, in the NTP study, incidence of adenomas in the mouse liver and in the rat kidney were significantly increased, to about the same extent that forestomach papillomas were increased.

In light of the issues concerning the gavage dose method and the lack of a human forestomach, the PHG document should more fully justify its reliance on the forestomach data. For example, perhaps it is logical to consider the tissue site at which the highest chemical concentration would exist. For the gavage bolus delivery, in rodents that tissue is the forestomach, whereas in humans it might be the stomach. If there is no unique feature of the rodent forestomach (as opposed to the human stomach) that somehow makes the forestomach exquisitely more sensitive to carcinogenesis, then it is appropriate to consider forestomach carcinoma incidence.

Non-Drinking Water Exposure: The PHG document estimated that inhalation exposure is essentially equivalent to ingesting another 2 L/day of water containing TCP. However, two items indicate that, in general, daily inhalation of TCP vapor would contribute substantially less than ingesting 2 L of water containing TCP.

First, on page 6, the PHG document stated that "the vadose soil compartment was loaded with various concentrations of 1,2,3-trichloropropane and the [CALTOX] model was run to determine average in-house exposures ...". The assumption seems to have been that if

drinking water contains TCP, then so must the soil water surrounding a single-family residence. The two media need not be linked. The source of drinking water delivered by a distribution system could be far removed from the residence, which is the typical circumstance in suburban and urban areas. In addition, a substantial portion of the population does not live in single-family dwellings. Residential units in multi-story apartment buildings are not subject to the same degree of vapor intrusion as are single-family dwellings with below-grade basements.

Second, on page 6, the PHG document stated that showering would be the primary source (and perhaps the only meaningful source) of TCP exposure other than drinking water. In this regard, the document seems to have ignored the 2003 Tancrède, et al., study (cited in CICAD 56) titled "Volatilization of Volatile Organic Compounds from Showers – I. Analytical Method and Quantitative Assessment (Atmospheric Environment, Vol. 26A, pp 1103-1111). That study found that the fraction of TCP volatilized from shower water across three different temperatures (25 °C, 33 °C, 42 °C) was 20%, and that only 5% to 17% of the vaporized TCP could be recovered from air. The implication of the latter finding was that there was at least one mechanism other than ventilation that removed vaporized TCP from shower stall air. The net result is that only a small percent of TCP (1% to 4%) was both lost from the shower water and available for inhalation.

The Tancrède, et al., study did not report airborne TCP levels during showering. I made the following estimate. Consider a 3 ft × 3 ft × 8 ft shower stall (volume 2 m^3) with a 3 ft × 0.5 ft opening above the door. Air moves into the stall through half the opening (and out through the other half) at the low speed of 10 ft/min, such that the dilution air flowrate is 0.5 × 1.5 ft^2 × 10 ft/min = 7.5 ft^3/min (0.21 m^3/min). The shower water contains TCP at, say, 10 μg/L, and flows at the rate of 13.5 L/min (the supply rate used by Tancrède, et al.). Assume that as much as 10% of the TCP is available for inhalation at the rate of 0.10 × (13.5 L/min) × (10 μg/L) = 13.5 μg/min. Assume showering lasts 12 minutes (the study shower time). Given a 12-min shower and an air exchange rate of 0.1 min^{-1}, or (0.21 m^3/min) ÷ (2 m^3), a steady-state airborne concentration (64 μg/m^3) would not be attained. Instead, the 12-min time-weighted average airborne concentration in the stall would be 27 μg/m^3:

$$\text{12-min TWA} = \frac{1}{12}\int_0^{12} 64\left[1 - \exp(-0.1\times t)\right]dt = 27\ \mu g/m^3$$

If the person breathes at the rate of 1 m^3/hr, the TCP mass inhaled during the 12-min shower is 5.4 μg, of which 50% is absorbed from the lungs, or 2.7 μg. Because the same drinking water contains TCP at 10 μg/L (which is 100% absorbed), showering adds the drinking water equivalent of 0.27 L. If only 5% of the TCP in shower water becomes available for inhalation, or slightly more than reported in the Tancrède, et al., study, the drinking water equivalent is 0.14 L. Thus, whereas the PHG document assumed consumption of 4 L_{eq}/day of drinking water, the more appropriate value would be approximately 2.2 L_{eq}/day.

Issue #5 – Other Critical Information That Might Affect Risk Estimates: Although potential TCP inhalation exposure via showering was overestimated in the PHG document, other residential sources of emission from drinking water were not discussed. If TCP solubility in water decreases with increased temperature (the document does not discuss indicate how TCP solubility varies with water temperature), washing laundry in hot water and boiling water for cooking would be expected to release a greater fraction of the TCP as compared to showering. Depending on the rooms and the ventilation conditions in which these activities are performed, and the extent of these activities, TCP inhalation might assume equal if not greater importance than ingestion.

Issue #6 – Appropriateness of Considering Uncertainties: The PHG document lacked a formal uncertainty analysis, but I judge such an analysis is not needed because the estimation of carcinogenic potency was health-conservative. The document used carcinoma data for the most sensitive tissue site (the forestomach), and it used the 95% upper confidence limit on the estimate of carcinogenic potency. Uncertainty in current TCP exposures was not a factor, because the document sought to estimate the concentration in drinking water that corresponded to an acceptable excess risk, as opposed to estimating current risks based on current exposures. Given a fixed concentration in drinking water, the document did not consider the population variability in the average daily TCP intake; on the other hand, my sense is that the extent of such exposure variability is far less than the uncertainty in the estimate of carcinogenic potency.

Minor Comments:

I suggest the document include a short generic appendix (which might be used in other PHG documents) describing the general multi-stage model and the meaning of q_1^*. My understanding is that q_1^* is the upper 95% confidence limit on the estimate of q_1 (adjusted for background risk) based on the model:

$$R = 1 - \exp[-(q_0 + q_1 \times d + q_2 \times d^2 + \ldots)]$$

In turn, the "linear" incremental risk model ignores the power terms and uses:

$$R = 1 - \exp(-q_1^* \times d)$$

Absent this explanation, the document is unintelligible to a reader not versed in the standard way that OEHHA estimates carcinogen potency.

On page 23, the quantity LED_{10} was described as the "lower-bound of the dose associated with a 10% cancer risk," and on page 24 it was described as the "lowest estimate of the lower bound on the dose causing a 10 percent tumor incidence". My impression is that the LED_{10} is a lower confidence limit (perhaps the lower 95% confidence limit) on the daily dose causing an excess cancer risk of 10%. Because the LED_{10} is a statistical estimate, it should be precisely defined. However, I question why the LED_{10} quantity was used in the first place, which segues to the discussion below.

On page 24, the PHG document should explain why the cancer slope factor is based on the LED_{10} value rather than the q_1^* estimate. If linearity is being assumed, the q_1^* estimate should pertain to the dose-response line over the entire dose range (or at least up to the 10% risk value). Deriving a cancer slope factor based on the LED_{10} value seems an unnecessary ad hoc procedure. And for the female mouse forestomach carcinoma data, there is little difference between the values 24 $(mg/kg \cdot day)^{-1}$ [based on the LED_{10}] and 25 $(mg/kg \cdot day)^{-1}$ [equal to q_1^*].

The right-hand side of the equation for C shown on page 27 needs to be multiplied by the factor 1,000 μg/g to yield the unit μg/L.

For clarity, the "ppm" and "ppb" units for TCP in water should be identified as, respectively, ppm weight-by-volume and ppb weight-by-volume. Given unit density for water, the ppm and ppb metrics might also be identified as weight-by-weight.

On page 3, the document states that TCP's vapor pressure of 3.1 mm Hg at 25 °C constitutes "relatively high volatility". Relative to other organic solvents, 3.1 mm Hg does not constitute high volatility; for example, at 25 °C, benzene's vapor pressure is 95 mm Hg. Perhaps the document means to say that TCP will substantially volatilize from water relative to other organic solvents but, here again, the air-to-water partition coefficient (K_{AW}, the "dimensionless" Henry's Law constant) for TCP is 0.013 according to Table 1, page 3, whereas it is 0.22 for benzene. As an editorial suggestion, it would be more useful for Table 1 to list $K_{AW} = 0.013$ rather than $H = 3.17 \times 10^{-4}$ $m^3 \cdot atm/mol$. It is simpler to compute TCP's partitioning between air and water at low concentrations using K_{AW} given:

$$K_{AW} = \frac{\text{Concentration in air (mol/L)}}{\text{Concentration in water (mol/L)}}$$

The conversion from H to K_{AW} is provided by:

$$K_{AW}\left(\frac{\text{L water}}{\text{L air}}\right) = \frac{H\left(\frac{m^3 \cdot atm}{\cdot mol}\right)}{8.205 \times 10^{-5}\left(\frac{m^3 \cdot atm}{mol \cdot K}\right) \times T\,(K)}$$